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**Optimization of analgesia for piglet castration under
isoflurane anaesthesia with parenteral butorphanol,
meloxicam or intratesticular lidocaine**

Inaugural-Dissertation

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

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2017

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1. Summaries

1.1 Summary

This blinded prospective study investigated analgesic effects of intramuscular (IM) butorphanol, meloxicam or intratesticular (IT) lidocaine for castration of 7-14 days old piglets under isoflurane anaesthesia. 66 piglets were randomly injected with: meloxicam IM (0.4 mg/kg; group M), butorphanol IM (0.2 mg/kg; group B), or both (group BM) 20 minutes prior to castration, or lidocaine IT (4 mg/kg (group ML4) or 8 mg/kg (group ML8)) together with meloxicam IM (0.4 mg/kg) under anaesthesia with 1.8% end-tidal isoflurane. Heart rate, respiratory rate, mean arterial blood pressure and end-tidal carbon dioxide were recorded. Anaesthesia quality was scored and postoperative behaviour assessed.

As butorphanol caused unacceptable side effects, its use was stopped. Group M showed worse anaesthesia quality than ML4 and ML8 (higher incidence of movements: 11/17, 3/18 and 4/17, respectively). There was no significant difference between groups regarding parameters measured during castration. Postoperative behaviour did not differ between groups.

For castration of 7-14 days old piglets under isoflurane anaesthesia, IT lidocaine provides side effect free additional analgesia.

Keywords: local anaesthesia, inhalation anaesthesia, swine

1.2 Zusammenfassung

Diese prospektive Blindstudie untersuchte den analgetischen Effekt von intramuskulärem (IM) Butorphanol, Meloxicam oder intratestikulärem (IT) Lidocain für die Kastration von 7-14 täglichen Ferkeln unter Isoflurananästhesie. 66 Ferkel wurden zufällig injiziert mit: Meloxicam IM (0.4 mg/kg; Gruppe M), Butorphanol IM (0.2 mg/kg; Gruppe B), oder beidem (Gruppe MB) 20 Minuten vor Kastration, oder Lidocain IT (4 mg/kg (Gruppe ML4), oder 8 mg/kg (Gruppe ML8)) und Meloxicam IM (0.4 mg/kg) unter 1.8% end-tidaler Isoflurananästhesie. Herzfrequenz, Atemfrequenz, mittlerer arterieller Blutdruck und end-tidales Kohlendioxid wurden dokumentiert. Die Anästhesiequalität wurde beurteilt und das postoperative Verhalten beobachtet.

Butorphanol verursachte unakzeptable Nebenwirkungen und seine Verwendung wurde gestoppt. Gruppe M zeigte schlechtere Anästhesiequalität als ML4 und ML8 (höhere Inzidenz von Bewegungen: 11/17, 3/18 und 4/17). Übrige intraoperative Parameter zeigten keine signifikanten Unterschiede und beim postoperativen Verhalten wurden keine Unterschiede zwischen den Gruppen erkannt. Für die Kastration von 7-14 täglichen Ferkeln unter Isoflurananästhesie bietet IT appliziertes Lidocain eine zusätzliche, nebenwirkungsfreie Analgesie.

Stichworte: Lokalanästhesie, Inhalationsanästhesie, Schwein

2. Introduction

In Switzerland, 1.3 millions male piglets are castrated yearly, 75% under inhalation anaesthesia (Enz et al., 2013). Isoflurane is a volatile agent providing fast and save induction of anaesthesia in pigs (Hodgson, 2007). As it lacks analgesic properties (Petersen-Felix et al., 1995) it does not reduce stress response to castration (Schulz, 2007). With additional administration of a non-steroidal anti inflammatory drug (NSAID) such as meloxicam, stress response is reduced (Schulz, 2007). Piglets receiving meloxicam further show less pain related behaviour during surgery as well as postoperatively (Zöls, 2006; Hansson et al., 2011). However in a Swiss survey 22% of piglets castrated under isoflurane anaesthesia including meloxicam, showed movement during castration (Enz et al., 2013). Studies performed in Germany showed even higher numbers of insufficient depth of anaesthesia ranging from 23 - 34% (Steigmann, 2013; Schwennen et al., 2016).

To improve analgesia during castration under inhalation anaesthesia, local anaesthesia could be used. With local anaesthesia, blockade of nociceptive transmission should result in pain relief (Vandermeulen, 2000). It has been shown in awake piglets, that intraoperative vocalisation and defence movements are reduced using intratesticular (IT) or subcutaneous lidocaine, in comparison to no analgesia (Leidig et al., 2009; Hansson et al., 2011). In piglets castrated under halothane anaesthesia, mean arterial blood pressures raised significantly less with local anaesthesia and fewer pain-related changes in EEG were seen (Haga & Ranheim, 2005). Otherwise, literature concerning perioperative pain reduction using local anaesthesia for castration of awake piglets is controversial. Procaine IT in comparison to no analgesia for castration of awake piglets did not result in a reduction of neuroendocrine stress response post operatively, or even an increased stress response was described (Zöls, 2006; Zankl et al., 2007). In contrast, piglets receiving lidocaine IT compared to no analgesia or meloxicam only, showed a lower increase in postoperative plasma cortisol levels (Kluivers-Poodt et al., 2012). An even better outcome was seen in a recently published study using a combination of parenteral meloxicam and IT and subcutaneous lidocaine (Bonastre et al., 2016).

Another option to improve perioperative analgesia is the use of butorphanol, a central acting opioid (Riviere & Papich, 2009). Under injection anaesthesia, butorphanol (0.2 mg/kg IM) in combination with different drugs improved anaesthesia quality and provided optimised perioperative analgesia (Nussbaumer et al., 2011).

The aim of this study was to investigate the effects of additional IM butorphanol or IT lidocaine on the intraoperative response to castration in piglets under isoflurane anaesthesia including parenteral meloxicam as well as the effect on postoperative behaviour.

3. Animals, material and methods

3.1 Animals

The study was approved by the veterinary office of the Canton of Zurich (081/2016).

66 male mixed breed piglets aged between 7 and 14 days were included in this study and by means of an online randomization tool allocated to 5 groups.

3.2 Material and methods

Twenty minutes prior to castration, Group M was injected meloxicam 0.4 mg/kg (Metacam®, Boehringer Ingelheim, Germany) IM, Group B received butorphanol 0.2 mg/kg (Butomidor®, Streuli, Uznach, Switzerland) IM and Group MB received meloxicam and butorphanol (0.4 mg/kg, respectively 0.2 mg/kg) IM. Group ML4 and ML8 received either 4 mg/kg or 8 mg/kg lidocaine (Lidocain 2%®, Streuli, Uznach, Switzerland) IT together with meloxicam (0.4 mg/kg) IM just before castration, under inhalation anaesthesia. A person not involved in the study judgement performed all injections. The person judging the quality of castration and recording the vital parameters was blinded to group allocation through the entire trial.

All male piglets from each litter were separated from females. The person responsible for drug administration estimated the weight of the piglets and administered the drugs in a random order (in groups M, B, and MB). After 20 minutes, anaesthesia of the first piglet was induced by mask with 5% isoflurane (initial vaporizer setting, Attane™, Piramal Healthcare, Limited India) and a flow of 2 L/min of O₂. The piglet was placed in dorsal recumbency and instrumented with ECG, pulse oxymetry (SpO₂), oscillometric blood pressure measurement device (Dinamap Carescape™ V100 vital sign monitor, GE Healthcare) with a cuff positioned over the right front limb metacarpal artery, and a capnograph tube, which was placed 0.5 cm inside the piglet's nostril. Two minutes after the onset of isoflurane the following parameters were recorded: heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MAP), end-tidal CO₂ (EtCO₂) and end-tidal isoflurane (EtIso). Subsequently, the isoflurane vaporizer was adjusted to maintain EtIso of $1.8 \pm 0.1\%$, the fresh gas flow of O₂ remained constant. Piglets of group ML4 and ML8 were then injected lidocaine IT and meloxicam IM.

One minute thereafter, the blinded observer judged reaction to insertion of a 22G needle into each testicle (performed in duplicate) with a scoring system (table 1) described by Berchtold (Berchtold, 2015). Simultaneously, the vital parameters above mentioned were recorded.

If number of movements or intensity of movement was <2, castration was performed (see table 1). Otherwise an additional minute was deferred and the same procedure was repeated.

This was carried out for 10 minutes in one-minute intervals. If the piglet still showed a score ≥ 2 , butorphanol 0.2 mg/kg IM was administered and the piglet castrated.

During castration the following steps were distinguished: 1. incision above both testicles, without opening the processus vaginalis (defined as “cut”), 2. exteriorization of testicles (“exteriorization”) and 3. “emasculatation” performed simultaneously in both testicles. During each step, monitored parameters and movements were recorded. If scores of movement were ≥ 2 in any of these three steps, an additional minute was deferred before the next step. The time from induction of anaesthesia until emasculatation, as well as the time from the injection of lidocaine until cut, was recorded. At the end of the castration, the degree of postoperative bleeding (0 = no bleeding, 1 = mild bleeding, 2 = moderate bleeding) was judged. The piglets were weighted and placed back to the other male piglets. Time until full recovery (standing and 4 steps) was measured.

After 24 hours the piglets underwent a pain assessment adapted from Stark (Stark, 2014). For this purpose each piglet was observed during a 10-minute period and events such as playing (seconds), lying (seconds), time at the teats (seconds) and the amount of pain specific behaviours (quantity) were noted (table 2). Additionally a visual analogue scale (VAS) was accomplished to judge the general condition of the piglets.

Table 1: Scoring system used to judge depth of anaesthesia by means of scoring occurring movements during all steps of castration (Berchtold, 2015).

Score	Number of movements	Score	Intensity of movement
0	No movement	0	No movement
1	One movement, twitch	1	Movement of one limb, movement of the head
2	Repeated movement, >2 twitches	2	Movement of more than one limb, continuous movement of the head
3	Continuous movement	3	Same as 2 including vertebral column
		4	Same as 3, but stronger reaction

Table 2: Post operative pain assessment adapted from Stark (Stark, 2014).

	Non specific behaviour
Time at the teats	Time at the teats, suckling, massaging the teats (seconds)
Lying	Motionless lying in sternal recumbency, sternum touching the ground (seconds)
Playing	Running, sudden jumping up, animating other piglets (seconds)
	Pain specific behaviour
Tail movement	Vertical or horizontal movement of the tail, >3 movements
Pain behaviour	Kneeling Scratching (quantity)
Change of position	Change in position out of lying or sitting, not counted when induced by another piglet (quantity)
	Social behaviour
Isolation	Stay at least two piglet length away from the other piglets. Only counted when desynchronisation is present (quantity)
Desynchronisation	Activity distinguishes from at least 75% of the other piglets (quantity)

3.3 Statistical analysis

A power analysis with a power of 0.8 showed, that to test if the incidence of defence movements during castration can be reduced with lidocaine from 50% to 0%, 11 piglets were considered necessary (WinEpiscope®).

All results were compiled in a spreadsheet (Microsoft Office Excel 2010) and extracted in NCSS 10 (NCSS Statistical Software, Kaysville, USA) for statistical analysis. All continuous parameters were tested for normal distribution. For nonparametric data a Kruskal-Wallis test was used. If significance was obtained, a post hoc analysis with a Mann Whitney U with a manual Bonferroni correction was performed to find the difference between groups.

Significance for the incidence of defence movement was tested with a fisher exact test. For this analysis, piglets were either classified as 0 = no movement, or 1 = movement during the castration. For scores of defence movement, all scores were summed up from the time-point 1 minute until emasculation and the total score was compared. Statistical significance was considered as $p < 0.05$. For the post hoc analysis $p < 0.017$ was considered significant, as three comparisons were performed.

4. Results

All piglets survived the study. One piglet was euthanized due to inguinal hernia one day after castration. In the first 17 piglets that were castrated, unexpected adverse effects such as salivation (1), cyanosis (1), dyspnoea (1), vomiting (1), and paddling before (1), during (1) and after (3) castration as well as excitatory behaviour (2) was seen in 5 animals. It was speculated that butorphanol caused these symptoms. The dosage of butorphanol was then adjusted to 0.1 mg/kg IM. The same adverse effects were present in additional 5 piglets. The person responsible for drug administration revealed, that 10 out of 14 piglets, which received butorphanol, either alone or in combination with meloxicam, experienced side effects, while no piglet out of the other three groups (total of 18 piglets) showed similar symptoms. Therefore, butorphanol was withdrawn from the study after the castration of 32 piglets and the remaining piglets from group B and MB were reallocated to the residual three groups. Finally 52 piglets were included in the study, 17 in group M, 18 in group ML4 and 17 in group ML8.

Results are presented with median (interquartile range; range). There was no significant difference between groups in age, estimated weight, scaled weight, time from induction of anaesthesia until emasculation and time from injection of local anaesthesia until cut (table 3). Also no difference was seen between the estimated and the scaled weight of the piglets ($p=0.69$). EtIso was maintained within predetermined range of $1.8 \pm 0.1\%$ during castration. There was no significant difference in EtCO₂ between the groups at any time point. In group M (11/17), piglets showed significantly higher incidence of movement than in group ML4 (3/18; $p=0.01$) and ML8 (3/17; $p=0.04$). Number of defence movements were significantly different, but scores were only significantly different in group M (1 (0-2.5; 4) compared to group ML4 (0 (0-0; 4), $p=0.012$), but not to ML8 (0 (0-0; 7), $p=0.024$) after the Bonferroni correction. For the intensity of defence movement no significance compared to the control group was obtained after the Bonferroni correction (group M 2 (0-3; 6), group ML4 0 (0-0; 6), $p=0.018$, group ML8 0 (0-0; 10), $p=0.025$).

The vital parameters HR, RR, SpO₂ and MAP were not significantly different between groups at any time point.

There was no significant difference between groups regarding degree of postoperative bleeding or time until full recovery (table 3).

The effectively used dose (based on the scaled weight) of lidocaine in group ML4 was 3.852 mg (3.15-4.286; 3.235) and in group ML8 8 mg (6.667-8.421; 6.956). No adverse effects of lidocaine were seen.

No significant difference was seen in the VAS between groups. As the results of the postoperative behaviour assessment were inhomogeneous with wide distributions and the assessment method retrospectively did not seem appropriate, no more details are shown.

Table 3: Age, estimated weight, scaled weight, time from induction of anaesthesia until emasculation, time from injection of local anaesthesia until cut, time until full recovery and amount of post operative bleeding of group M, ML4 and ML8. Numbers are given as median (interquartile range; range).

	Group M	Group ML4	Group ML8	p-value
Age (days)	9 (8-9; 1)	9 (8-9; 1)	9 (8-9; 1)	0.39
Estimated weight (kg)	3 (2-4; 4)	3 (2.5-3.5; 3)	3.5 (2.5-3.5; 3)	0.96
Scaled weight (kg)	3.2 (2.35-3.5; 3.5)	2.9 (2.7-3.8; 3.2)	3.3 (2.8-3.7; 1.8)	0.76
Time induction anaesthesia – emasculation (sec)	420 (373-439.5; 190)	379 (359-410; 184)	410 (384-450; 239)	0.27
Time injection lidocaine – cut (sec)	125 (112.5-138; 31)	120 (115-129; 154)	120 (115-150; 110)	0.80
Time until full recovery (sec)	142 (103-182; 212)	180.5 (116-220; 376)	181 (143-225; 334)	0.74
Postoperative bleeding	1 (0-1; 2)	0 (0-1; 2)	0 (0-1; 2)	0.70

5. Discussion

As with the current Swiss standard anaesthesia for piglet castration with isoflurane and meloxicam 14-34% of piglets show purposeful movement in response to surgery (Enz et al., 2013; Steigmann, 2013; Schwennen et al., 2016), the current study investigated further analgesics in order to reduce unnecessary suffering of piglets undergoing castration. In the present study, the additional use of IT lidocaine reduced pain-related defence movements during castration under inhalation anaesthesia from 65% to 17-18% independent of dose rate (4 mg/kg and 8 mg/kg) used. Incidence of movements of group M in the present study was higher than previously published (Enz et al., 2013; Steigmann, 2013; Schwennen et al., 2016). This discrepancy may have occurred, as the authors of the present study recorded any kind of movement and the piglets were not fixed at all, whereas other authors judged mild movements as unconscious reflexes and not pain related and piglets were fixed with a commercially available castration system. The results of our study are in agreement with previous studies that showed a beneficial analgesic effect of IT lidocaine for piglet castration (Hansson et al., 2011; Kluivers-Poodt et al., 2012). Studies with procaine however concluded, that local anaesthesia was not beneficial for piglet castration, as increased cortisol concentrations thereafter were detected (Zöls, 2006; Zankl et al., 2007). The administration of procaine IT to conscious pigs was additionally deemed painful (Rittershaus, 2009). Also human data showed that the injection of lidocaine is painful (Wago et al., 2016). Therefore, in the present study, IT lidocaine was applied only under inhalation anaesthesia. Lidocaine is rapidly distributed to the spermatic cord when administered IT and reaches peak concentrations 3 minutes after injection in piglets (Ranheim et al., 2005). In the present study median time necessary from injection of lidocaine until start of castration was 120 seconds. Therefore we recommend to wait at least 2-3 minutes from lidocaine injection to castration. A study investigating the plasma concentration of lidocaine, which induces toxic effects marked by seizures in newborn piglets showed, that plasma levels of 40 mg/L lidocaine cause seizures. This corresponds to 30-60 mg of lidocaine for piglets of 1.6 kg administered intravenously (Satas et al., 1997). Even though these dosages are higher than the dosages used in the present study, we wanted to test two different dosages of lidocaine to ensure safety of 8 mg/kg lidocaine and to detect any toxic effect. No signs of toxicity were observed in the present study and the application of either dose tested IT is considered safe.

Anaesthesia induction was performed with a fresh gas flow of 2 L/min O₂ and 5% isoflurane vaporizer setting, which is the dose used in the commercially available inhalation anaesthesia devices. In piglets 1 MAC isoflurane is 1.4% EtIso (Lerman et al., 1990). MAC is a number

that gives an estimate of dose rates of inhalant anaesthetics necessary to maintain anaesthesia. 1 MAC is the number at which 50% of test animals do not react with purposeful movement to a defined stimulus (Levionnois et al., 2009). It is a concentration of inhalant anaesthetic not sufficient to perform surgery in any case and certainly not for surgical castration, therefore the concentration of inhalant anaesthetic was determined, where 95% of patients would not react to a surgical incision, which was found to be 5-40% higher than 1 MAC for humans (de Jong & Eger, 1975). For this reason we chose to provide 1.3 MAC, which corresponds to 1.82% EtIso for maintenance of anaesthesia during castration, as it was described to be sufficient plane of anaesthesia for a surgical stimulus in pigs (Hodgson, 2006).

The administration of butorphanol led to adverse effects and was therefore withdrawn from the study. To date, pronounced adverse effects of 0.2 mg/kg butorphanol, as noted in the present study, have not been reported in piglets. Nussbaumer et al. described mild excitatory behaviour in some cases during the induction of anaesthesia using a combination of ketamine, azaperone and butorphanol IM for castration in pigs of different ages (Nussbaumer et al., 2011). Bettschart-Wolfensberger et al. reported paddling in two out of 28 nine weeks old pigs receiving azaperone, butorphanol, ketamine and meloxicam (Bettschart-Wolfensberger et al., 2013). None of these authors related these side effects to butorphanol. Other authors used butorphanol in a combination with various drugs in pigs of different ages and did not report any adverse effects (Nussbaumer et al., 2008; Heinonen et al., 2009). As the described symptoms in the present study appeared in piglets that had not received any other drug, we suspected butorphanol to be the cause and therefore first reduced the dose and then withdrew butorphanol from the study. The symptoms were not observed again. Contradictory to that, Courboulay et al. used butorphanol (0.1 mg/kg) in combination with meloxicam for castration of awake French piglets and did not report any adverse reactions (Courboulay et al., 2015). Genetic varieties could explain the discrepancy. In a separate study investigating the effect of butorphanol (0.2mg/kg IM), it was clearly shown, that butorphanol causes restlessness, vocalization and panting, as well as excitatory behaviour (Cap et al., 2017). In other species adverse effects of butorphanol are well described. While dysphoric behaviour is described in cats (Lascelles & Robertson, 2004), horses become ataxic and have increased locomotion (Sellon et al., 2001; Knych et al., 2013), whereas sheep become dysphoric and ataxic (Waterman et al., 1991). These adverse reactions to butorphanol administration warrant further investigation in piglets.

For the postoperative evaluation 24 hours after castration, the piglets were observed for ten minutes as described by Stark (Stark, 2014). When the study was designed this was the only

pain assessment described for this age category of piglets. In each litter observation was randomly done for a group of three piglets at the time. It was quickly discovered during the trial, that it depended which ten minutes were evaluated. Sometimes these 10 minutes were spent with lying or drinking whereas 10 minutes later the litter was active and played. Some of the pain specific behaviour was also observed in not castrated piglets of the litter and therefore we conclude that the scoring system used was not appropriate to properly detect differences in postoperative pain between the groups. A newly available method to score postoperative pain, the piglet grimace scale, is an alternative that could be implemented in further investigations (Viscardi et al., 2017).

The authors conclude, that for castration of 7-14 days old piglets under isoflurane anaesthesia and parenteral meloxicam, perioperative analgesia is optimised by additional application of IT lidocaine. For optimal results at least two minutes have to elapse between local anaesthesia application and castration. No toxic side effects were seen and it is concluded that lidocaine can be used safely in daily practice.

6. Literature

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7. Acknowledgement

First of all I would like to thank my supervisor Prof. Dr. med. vet. PhD Regula-Bettschart-Wolfensberger. I was very grateful for her continuous support, her knowledge and motivation during my thesis. She always had an open ear and helped me with any kind of problems.

A special thanks goes to Veronika Cap. Her help during the trial was irreplaceable and without her friendship it would not have worked out. Her positive nature inspired me and the time we spent in the piggery was unforgettable.

I would like to acknowledge especially Simone Ringer, who supported me during the final phase of my thesis in a very valuable way. Additionally, I would like to thank Andrea Schwarz for the positive inputs on my presentation and my thesis.

Also, I would like to show my gratitude towards Sämi Ritter for the good care he took of the piglets of the trial.

To my family and friends I would like to express my appreciation for understanding and supporting my enthusiasm for my job. I would especially like to thank Simon Nogler for cheering me up if needed.

Last but not least I would like to thank the best possible team on earth - the A-Team! I could learn so much from each of you and you pushed me to the limit, which made me a better anesthesiologist. Thank you for this great time!

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